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***Full Length Research Paper***

# DESIGN AND CHARACTERIZATION OF DIVALPROEX SODIUM SOLID DISPERSION FOR EPILEPSY

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**Abstract**

Divalproex sodium is considered as the most important antiepileptic drug and widely used for treatment of epilepsy, bi-polar disorders and prophylaxis of migraine. The major problem with this drug is its poor solubility in biological fluids, which results into poor bioavailability after oral administration. Thus, solid dispersions (SDs) of Divalproex sodium were prepared using Hydroxy propyl methyl cellulose (HPMC), Polyethylene glycol (PEG 6000) and Polyvinyl pyrolidine (PVP K30) to increase its aqueous solubility. SDs of Divalproex sodium was prepared by solvent evaporation method with the ratio of drug and polymers were 1:1. The prepared solid dispersions were subjected for % yield, drug content and infrared (IR) spectroscopic studies and solubility studies. The FTIR results shows absence of significant drug-carrier interaction. *In vitro* release profiles of all SDs were evaluated and also studied against pure Divalproex sodium. It was observed that faster dissolution was found by solid dispersion containing Drug:HPMC. This may due to hydrophilic nature of the carrier and increase in wettability in solid dispersion. Thus it was concluded that SDs of Divalproex sodium could be beneficial for the treatment of epilepsy with improved bioavailability after oral administration.

**Keywords:** Divalproex Sodium, Polymers, Solid Dispersion, In-vitro release, Epilepsy.



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## INTRODUCTION

Oral bioavailability of drugs depends on its solubility and/or dissolution rate, therefore major problems associated with these drugs was its very low solubility in biological fluids, which results poor bioavailability after oral administration (Sekiguchi, 1961; Chiou, 1971; Brahmankar and Jaiswal, 1995; Swarbrick 2002; Leunner, 2000). A drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption (Golderg, 1966). Therefore, pharmaceutical researchers' focuses on two areas for improving the oral bioavailability of drugs include: (i) enhancing solubility and dissolution rate of poorly water-soluble drugs and (ii) enhancing permeability of poorly permeable drugs. It has been reported that nearly 40% of the new drug molecules were discovered as poorly water soluble (Prentis, 1988; Arunachalam, 2010). Unfortunately, many of these potential drugs are abandoned in the early stages of development due to the solubility problems. Therefore it is important to overcome the solubility problems of these insoluble drugs with improved potential therapeutic effects (Ford, 1986).

So far various efforts have been made to enhance the dissolution rate of drug such as salt formation, micronization and addition of solvent or surface active agents. Solid dispersion (SD) is one of such methods which involves a dispersion of one or more active ingredients in an inert carrier or matrix in solid state prepared by melting, dissolution in solvent or melting-solvent method (Chiou, 1971; Shah, 2007). Among the various approaches to improve solubility, the solid dispersion (SD) technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly soluble drugs because it is simple, economic, and advantageous (Dannenfelser, 2004). Since 1960, it has been an active area of research that the formulation of drugs with low aqueous solubility using solid dispersion technology (Noyes, 1897). Solid dispersion means a group of solid products consisting of at least two different components, generally a hydrophilic inert carrier or matrix and a hydrophobic drug. The carrier can be either crystalline or amorphous in nature. Most commonly used carriers for the preparation of SDs are different grade of polyethylene glycols (PEGs). The first drug whose rate and extent of absorption was significantly enhanced using the solid dispersion technique was sulfathiazole by Sekiguchi and Obi (Sekiguchi, 1961).

This technique has been used by many researchers/scientists for a wide variety of poorly aqueous soluble drugs to enhance the solubility of the drugs and hence bioavailability (Van Drooge, 2006). Poorly soluble drugs represent a problem for their scarce availability related to their low dissolution rate. The major drawback of low aqueous solubility is delays its absorption from the gastrointestinal tract. Solubility behavior of a drug is one of the key determinants of its oral bioavailability. Noyesh-Whitney equation provides some hints as to how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oral availability (Sridharan, 2002 and Lakhani, 2012). Where, dC/dt - is the rate of dissolution, A -is the surface area available for dissolution, D - is the diffusion coefficient of the compound, Cs- is the solubility of the compound in the dissolution medium, C -is the concentration of drug in the medium at time t and h - is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound. Epilepsy is abnormal, high frequency electrical discharge in brain characterized by transient episode (seizure) with or without loss of consciousness and characteristic body movement (convulsion). Globally epilepsy is the third most common neurological disorder after cerebrovascular and Alzheimer's disease. About 10 percent of the population will have at least one seizer in their life time (Ravi Chaudhari, 2015).

Divalproex sodium is a unique preparation consisting of sodium valporate and valporic acid in 1:1 molar relationship and formed during the partial neutralization of valproic acid with 0.5 equivalent of sodium hydroxide. Chemically, it is designated as sodium hydrogen bis (2-propylpentanoate) (Tachibana, 1965). Besides its role as a broad spectrum antiepileptic, used for the treatment of bipolar disorder, it is prescribed as antimigraine prophylactic agent for migraine. Divalproex sodium appears to act by multiple mechanisms: Prolongation of Na+ channel inactivation, augmentation of release of inhibitory transmitter GABA by inhibiting its degradation (Xie, 2009). Considering the above factors a novel solid dispersion approach was proposed in the present study wherein the poorly soluble divalprox sodium can be solid dispersed that improves dissolution and its absorption. So far no scientific reports are available on the development of solid dispersion of divalproex sodium. Hence an attempt has been made for its development.

## MATERIALS AND METHODS

Divalproex sodium was obtained as a gift sample from Micro labs, Hosur, Bangalore (India). Polyvinyl pyrrolidone K30 (PVP K30), Polyethylene glycol 6000 (PEG 6000) were obtained from Moly Chem, Mumbai (India). Hydroxy propyl methyl cellulose (HPMC), Acetone, Hydrochloric acid were procured from Loba Chemie Pvt Ltd, Mumbai (India). Methanol was purchased from Himedia Laboratories Pvt, Ltd, Mumbai (India). All other reagents and solvents used were of analytical grade.

### Preparation of physical mixture of solid dispersions

The formula for physical mixture was given in Table.1. Physical mixtures were prepared by mixing the appropriate amount of Divalprox sodium and Polyvinyl pyrrolidone K30 (PVP K30), Polyethylene glycol 6000 (PEG 6000) and Hydroxy propyl methyl cellulose (HPMC) in mortar and pestle separately and passed through sieve # 60. The resulted product was stored in desiccator to carry out further analysis (Ravi Chaud, 2015).

**Preparation of solid dispersion**

Solid dispersions of Divalprox sodium were prepared by solvent evaporation method. The carriers such as PVP K30, PEG 6000 and HPMC were added with the drug corresponding to ratio 1:1 was accurately weighed and mixed properly. This physical mixture was solubilized in a common solvent such as in ethanol (25 ml). The solvent was allowed to evaporate in hot air oven at 45°C ± 10°C. The process of evaporation was continued until the constant weight was obtained. This formulation was kept in dessicator for 24 h under vacuum. Then, solid dispersion formulation was pulverized using a porcelain mortar and pestle. The pulverized powder was classified using the sieves (size 60 # and 120 # mesh) and the particle size fraction of 100-250 mm was used for the study. Table 1.

**Evaluation of solid dispersions**

**Preliminary solubility studies of drug and solid dispersions**

An excess quantity of drug was placed in 20 ml capacity conical flasks containing accurately measured 10 ml of different solvents like distilled water (pH 7.0), pH 1.2 (0.1N HCl) and phosphate buffer ( pH 7.2) separately. The contents of the test tubes were sonicated for 20 min at room temperature in an ultra sonic bath (Bandelin sonorex). These test tubes were wrapped with aluminum foil at their open end, and kept for shaking at 75rpm for 30 hrs at 25±0.5°C in a mechanical shaker. The test-tubes were centrifuged for 20min at 1000rpm and supernatant liquid was collected and filtered using Watt's man filter paper. The filtrate was analyzed using spectrophotometrically (UV-1800 Shimadzu) at a λ max of 210nm after suitable dilutions. The amount of drugs dissolved in various solvents was estimated. The same procedure was repeated for solid dispersion of divalprox sodium with only distilled water (pH 7.4) as solvent (Lakhani, 2012).

**Fourier Transform Infrared Spectroscopy Studies (FTIR)**

To study the interaction between drug and polymers used in the preparation of formulation FTIR spectroscopy was carried out on test samples. FTIR spectrum of pure drug, physical mixtures and solid dispersions were recorded by using FT-IR 8400S (SHIMADZU, Kyoto, Japan) with the scanning range 4000 to 400$cm^{-1}$.

**2.3.3 % Practical Yield**

Percentage practical yield was calculated to know about percent yield or efficiency of any method, thus its help in selection of appropriate method of production. SDs were collected and weighed to determine practical yield (PY) from the following equation (Dannenfelser, 2004).

$$PY(\%) = \frac{\text{Practical Mass (Solid dispersion)}}{\text{Theoretical Mass (Drug + carrier)}} \times 100$$

**Drug content analysis**

Solid dispersion of equivalent to 10 mg was weighed accurately and transferred to 100 ml volumetric flask and dissolved in phosphate buffer pH 1.2. The volume was made up to the mark with phosphate buffer pH 1.2. The absorbance of the above solution was measured at 210 nm after suitable dilution using appropriate blank solution. The drug content of Divalprox sodium was calculated using calibration curve (Lakhani, 2012).

***In vitro* drug release studies**

The release profile of an entrapped drug predicts how a delivery system might function and gives valuable insight into its *in vivo* behavior. *In vitro* release profile for each solid dispersion as well as pure drug were performed using USP XXII type 2 dissolution apparatus (TDP-06P, Electro lab, Mumbai, India). Sample equivalent to 100 mg of Divalprox sodium was added to 900 ml phosphate buffer pH 1.2 at 37± 0.5ºC and stirred at 50 rpm. Aliquot of 5ml was withdrawn at time intervals of 5, 10, 15, 20, 30, 45, 60 and 90 min. The withdrawn volume was replaced with the same volume of dissolution medium in order to keep the total volume constant. The absorbance of the samples was measured using spectrophotometrically at λ max 210 nm after suitable dilution if necessary, using appropriate blank (Lakhani, 2012).

## RESULTS

PM1= Drug + Poly ethylene glycol 6000
PM2= Drug + Poly vinyl pyrolidine K30
PM3= Drug + Hydroxy propyl methyl cellulose
SD1 = Drug + Poly ethylene glycol 6000 solid dispersion
SD2 = Drug + Poly vinyl pyrolidine K30 solid dispersion
SD3= Drug + Hydroxy propyl methyl cellulose solid dispersion

**Preliminary solubility studies of drug and solid dispersions**

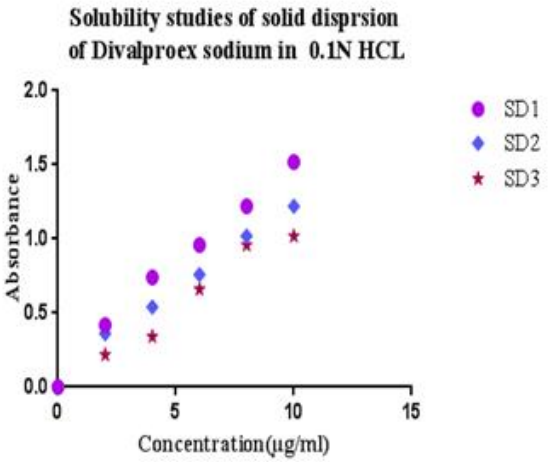


**Fig 1. Solubility studies on solid dispersion of divalproex sodium in 0.1N HCL**

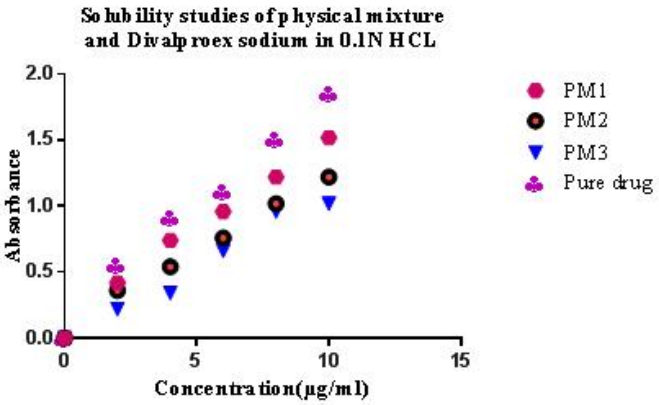


**Fig. 2. Solubility studies physical mixture and divalproex sodium in 0.1N HCL**

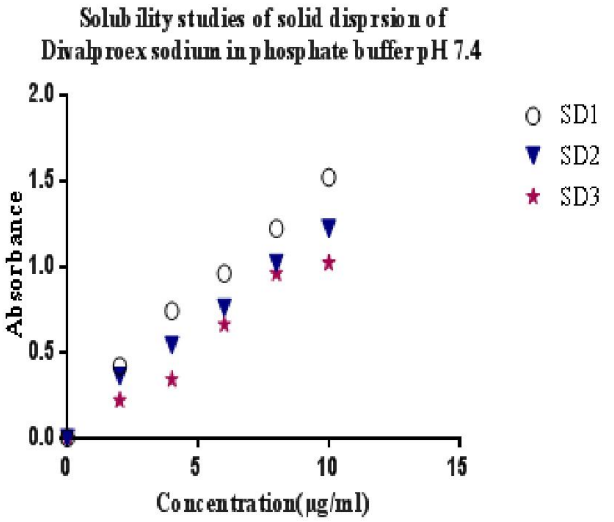


**Fig. 3. Solubility studies on solid dispersion of divalproex Sodium in Phosphate buffer 7.4**

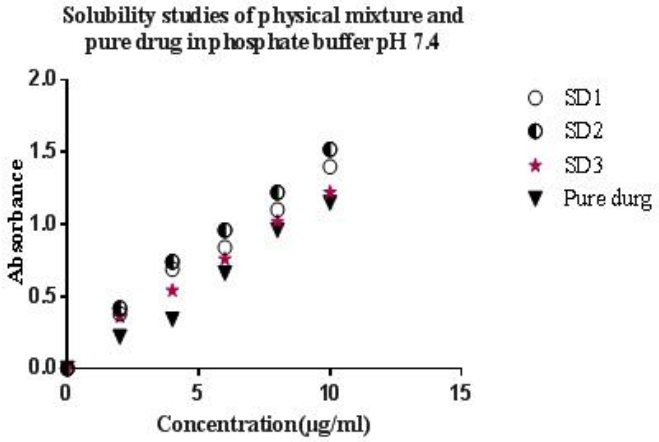


**Fig. 4. Solubility studies physical mixture and divalproex sodium in Phosphate buffer 7.4**

**Table. 1 Preparation of solid dispersion**

| S.NO | Formula code | Drug : Polymer (500:500mg) | Description of the product | Nature of formulation | Preparation method |
|---|---|---|---|---|---|
| **1.** | Pure drug | 1: - | ---------- | White amorphous powder | ---------- |
| **2.** | PM1 | 1:1 | Physical Mixture | Off-white sticky particle | ---------- |
| **3.** | PM2 | 1:1 | Physical Mixture | Off-white sticky particle | ---------- |
| **4.** | PM3 | 1:1 | Physical Mixture | Off-white sticky particle | ---------- |
| **5.** | SD1 | 1:1 | Solid dispersion | Solid sticky lumps | Solvent evaporation method |
| **6.** | SD2 | 1:1 | Solid dispersion | Solid sticky lumps | Solvent evaporation method |
| **7.** | SD3 | 1:1 | Solid dispersion | Solid sticky lumps | Solvent evaporation method |

## Fourier Transform Infrared Spectroscopy Studies (FTIR)

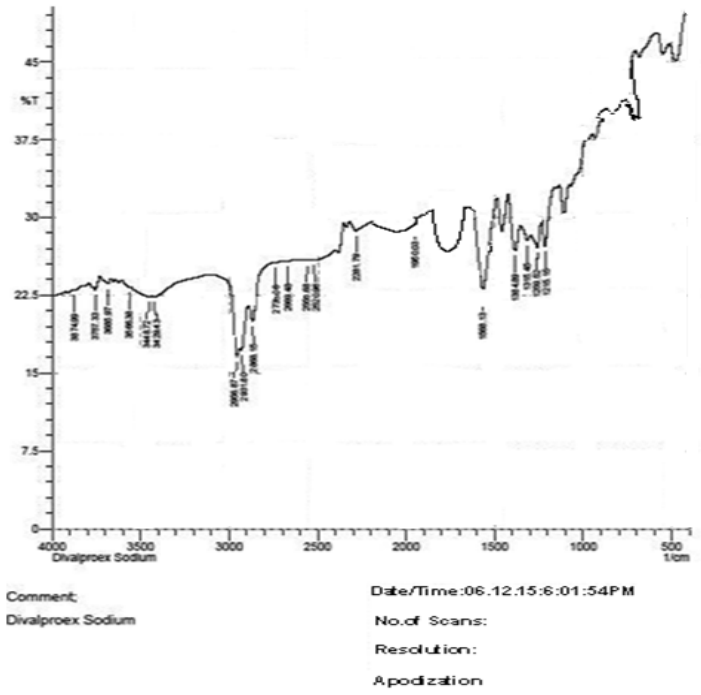


**Fig 5. FTIR of divalprox sodium**

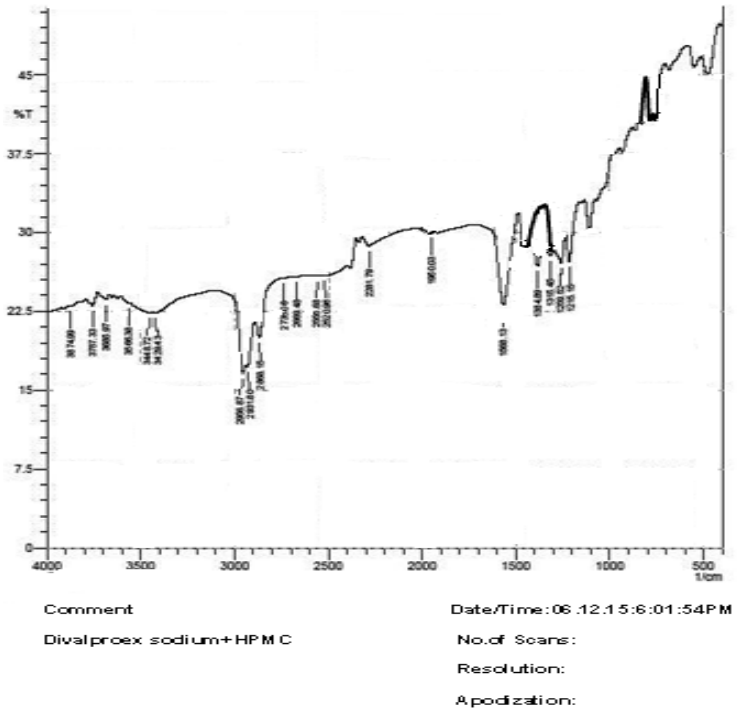


**Fig 6. FTIR of Solid dispersion (SD1)**

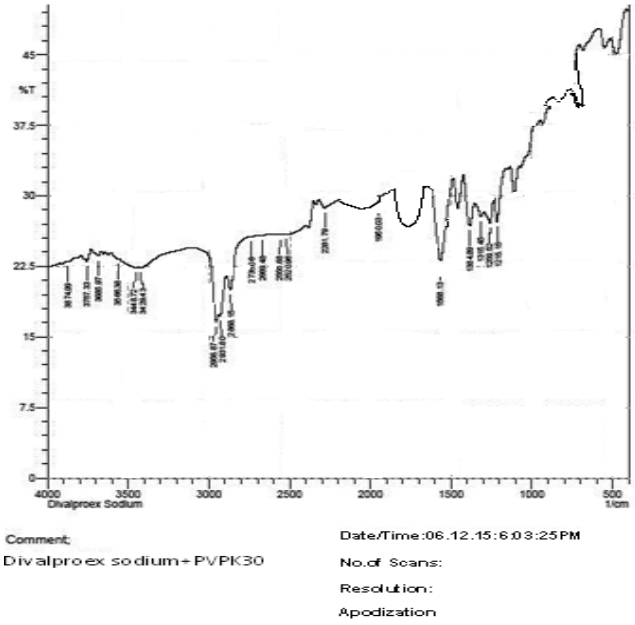


**Fig 7. FTIR of Solid dispersion (SD2)**

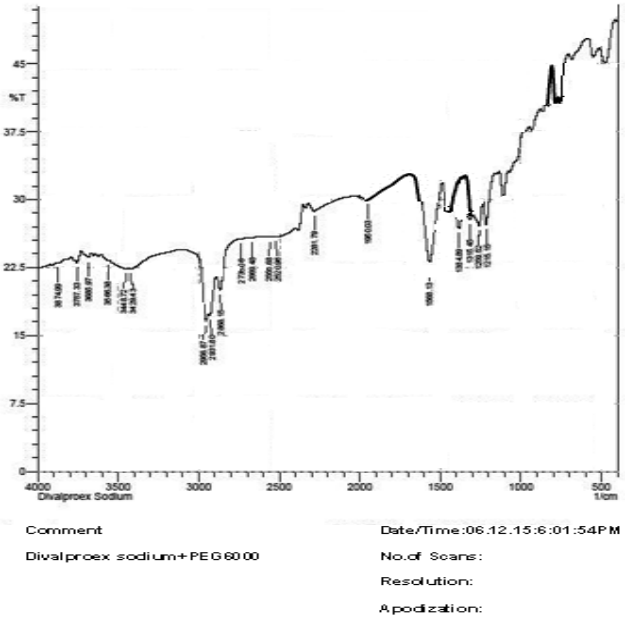


**Fig 8. FTIR of Solid dispersion (SD3)**

## DISCUSSION

SDs of Divalproex sodium was prepared by solvent evaporation method using carriers such as HPMC, PEG 6000, PVP K30 to improve the poor solubility of drug for the treatment of epilepsy. In our study, three formulations were prepared with the ratio 1:1of drug and polymers and were given in Table 1.

### Solubility studies of Divalproex sodium

The Solubility study of pure drug, physical mixture and SDs were performed in and pH 1.2 (0.1N HCL), pH 7.4 respectively. The results were given in Figs.1, 2, 3, 4 and it shows that there was an increase in the solubility of drug with the addition of carriers when compared with pure in both medium.

It may due to the hydrophilic nature of the carrier. The solubility of SDs with HPMC shows enhancing solubility than the other two polymers.

### Fourier Transform Infrared Spectroscopy Studies (FTIR)

FTIR of pure drug and solid dispersion was given in Figs. 5,6,7,8. Infra red studies was carried out to predict the interaction between drug and carrier used in formulation of solid dispersion by potassium bromide disc method using Infra red spectrophotometer.

The observed results shown that there were no interactions between pure drug and solid dispersion and both were compatible with each other.

**Drug content**

Drug content of all the SDs showed presence of high drug content with low standard deviations of results and the results were given in Table 2. It indicates that the drug is uniformly dispersed in the powder formulation. Therefore, the method used in this study appears to be reproducible for the preparation of SDs.

**Table. 2 Drug content and % Yield**

Mean±S.D, n=3

| S.No | Formulation code | % Drug Content | % Yield |
|---|---|---|---|
| **1.** | SD1 | 96.17±0.001 | 99.11±0.07 |
| **2.** | SD2 | 94.60±0.05 | 97.39±0.02 |
| **3.** | SD3 | 90.41±0.008 | 95.57±0.035 |

**% Practical Yield**

The percentage practical yield was found to be in the range of 95.57 to 99.11%. The maximum percentage practical yield was found to be 99.11% for SD1 and the results were given in Table 2.

***In-vitro* release study of divalpreox sodium**

Table 3,4,5,6 indicates the in vitro release studies of pure drug and SD1, SD2, SD3. *In vitro* release studies were performed to predict the best carrier used to improve the dissolution character of poorly soluble divalproex sodium 0.1N HCL .

The observed results reveal that there is gradual increase in the dissolution rate of divalproex sodium from all the solid dispersions when compared to pure divalproex sodium itself. From the *in vitro* drug release profile, the formulation SD1 containing HPMC (1:1 ratio of Drug: HMPC) shows higher dissolution rate when compared with other formulations in 0.1N HCL.

This may be attributed to the increase in drug wet ability, conversion of do drug from crystalline to amorphous form and solubilization of the drug due to hydrophilic carrier. The increase in dissolution rate is in the order of PEG 6000>PVPK30 >HPMC and the cumulative data was given Fig.9.

**Dissolution Studies**

**Table 3. % release of Divalproex sodium in 0.1N HCL**

Mean±S.D, n=3

| S.No | Time min) | Absorbance | Concentration (µg/ml) | Concentration in 900ml (mg/ml) | Loss to be added | Cummulative Amount of drug release | % drug release |
|---|---|---|---|---|---|---|---|
| 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 15 | 0.0675 | 2.25 | 2.025 | 0.002 | 2.025 | 20.25±0.01 |
| 3 | 30 | 0.0795 | 2.65 | 2.385 | 0.0028 | 2.38 | 23.8±0.021 |
| 4 | 45 | 0.1146 | 3.82 | 3.438 | 0.0034 | 3.43 | 34.3±0.032 |
| 5 | 60 | 0.1582 | 5.27 | 4.743 | 0.0047 | 4.74 | 47.4±0.006 |
| 6 | 75 | 0.1591 | 5.30 | 4.77 | 0.0047 | 4.77 | 47.7±0.055 |
| 7 | 90 | 0.1737 | 5.79 | 5.211 | 0.0052 | 5.21 | 52.1±0.076 |
| 8 | 105 | 0.1778 | 5.92 | 5.328 | 0.0053 | 5.32 | 53.2±0.015 |
| 9 | 120 | 0.2768 | 9.22 | 8.298 | 0.0082 | 8.29 | 82.9±0.091 |

**Table 4. % Drug release from solid dispersion in 0.1N HCL (SD1)**

Mean±S.D, n=3

| S.No | Time (min) | Absorbance | Concentration (µg/ml) | Concentration in 900ml (mg/ml) | Loss to be added | Cumulative Amount of drug release | % drug release |
|---|---|---|---|---|---|---|---|
| 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 15 | 0.0201 | 0.666 | 0.5994 | 0.00059 | 0.599 | 5.9±0.005 |
| 3 | 30 | 0.0240 | 0.802 | 0.720 | 0.00072 | 0.720 | 7.2±0.001 |
| 4 | 45 | 0.0308 | 1.026 | 0.9234 | 0.00092 | 0.923 | 9.2±0.002 |
| 5 | 60 | 0.0538 | 1.793 | 1.6137 | 0.0016 | 1.613 | 16.13±0.004 |
| 6 | 75 | 0.0854 | 2.846 | 2.5614 | 0.0025 | 2.561 | 25.61±0.035 |
| 7 | 90 | 0.1622 | 5.406 | 4.8654 | 0.0048 | 4.865 | 48.65±0.016 |
| 8 | 105 | 0.1802 | 6.006 | 5.4054 | 0.0054 | 5.405 | 54.05±0.041 |
| 9 | 120 | 0.3136 | 0.453 | 9.4077 | 0.0094 | 9.407 | 94.07±0.021 |

**Table 5. % Drug release from solid dispersion in 0.1N HCL (SD2)**

Mean±S.D, n=3

| *S.No* | *Time (min)* | *Absorbance* | *Concentration (µg/ml)* | *Concentration in 900ml (mg/ml)* | *Loss to be added* | *Cummulative Amount of drug release* | *% drug release* |
|---|---|---|---|---|---|---|---|
| ***1*** | *0* | *0* | *0* | *0* | *0* | *0* | *0* |
| ***2*** | *15* | *0.017* | *0.566* | *0.5094* | *0.0005* | *0.5094* | *5.09±0.023* |
| ***3*** | *30* | *0.0423* | *1.41* | *1.269* | *0.0012* | *1.269* | *12.69±0.01* |
| ***4*** | *45* | *0.0640* | *2.13* | *1.917* | *0.0019* | *1.917* | *19.17±0.001* |
| ***5*** | *60* | *0.1005* | *3.35* | *3.015* | *0.0030* | *3.015* | *30.15±0.006* |
| ***6*** | *75* | *0.1213* | *4.04* | *3.636* | *0.0036* | *3.636* | *36.36±0.001* |
| ***7*** | *90* | *0.1404* | *4.68* | *4.212* | *0.0042* | *4.212* | *42.12±0.001* |
| ***8*** | *105* | *0.1906* | *6.33* | *5.697* | *0.0056* | *5.697* | *56.97±0.005* |
| ***9*** | *120* | *0.2986* | *9.95* | *8.955* | *0.0089* | *8.955* | *89.55±0.011* |

**Table 6. % Drug release from solid dispersion in 0.1N HCL (SD3)**

Mean±S.D, n=3

| S.No | Time (min) | Absorbance | Concentration (µg/ml) | Concentration in 900ml (mg/ml) | Loss to be added | Cumulative Amount of drug release | % drug release |
|---|---|---|---|---|---|---|---|
| 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 15 | 0.0410 | 1.36 | 1.225 | 0.0012 | 1.225 | 12.25±0.032 |
| 3 | 30 | 0.0853 | 2.84 | 2.556 | 0.0025 | 2.55 | 25.5±0.041 |
| 4 | 45 | 0.1064 | 3.54 | 3.18 | 0.0031 | 3.18 | 31.8±0.035 |
| 5 | 60 | 0.1694 | 5.64 | 5.076 | 0.0050 | 5.076 | 50.76±0.073 |
| 6 | 75 | 0.1737 | 5.79 | 5.211 | 0.0052 | 5.211 | 52.11±0.041 |
| 7 | 90 | 0.1945 | 6.48 | 5.832 | 0.0058 | 5.83 | 58.3 ±0.054 |
| 8 | 105 | 0.2412 | 8.04 | 7.230 | 0.0072 | 7.23 | 72.3±0.002 |
| 9 | 120 | 0.3114 | 10.38 | 9.342 | 0.0093 | 9.34 | 93.4±0.017 |

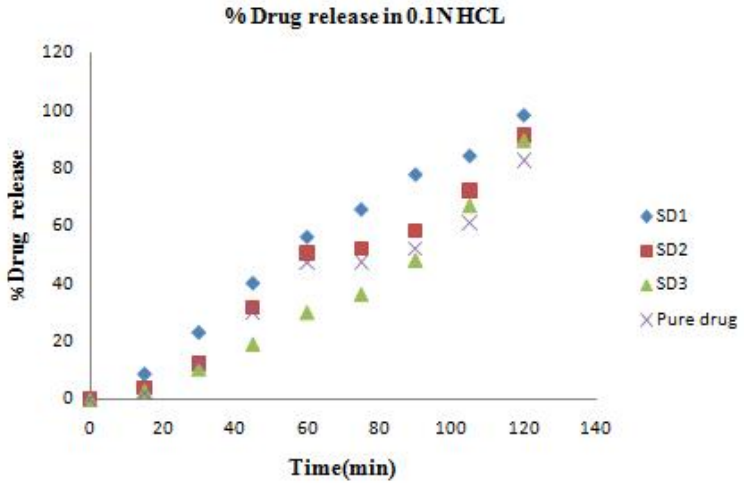


**Fig. 9.Comparative data of drug release in 0.1N HCL**

These observations indicate that the enhanced dissolution of SDs with HPMC possibly due to high solubility of the drug by the carrier in the medium, particle size reduction in the course of the solid dispersion preparation, polymorphic transformation of drug crystals and chemical interactions between drug and carrier when compared to other polymers.

## Summary

Solid dispersions of poorly water-soluble drugs with water-soluble carriers have been reduced the incidence of solubility problems and enhanced dissolution. The development of solid dispersion is a practically viable method to enhance bioavailability of poorly water-soluble drugs. Divalproex sodium is poorly soluble drug and is considered as the most important antiepileptic drug and widely used for treatment of epilepsy, bi-polar disorders and prophylaxis of migraine.

Considering the above factors solid dispersion approach was proposed in the present study wherein the poorly soluble divalproex sodium can be solid dispersed that improves dissolution and its absorption. So far no scientific reports are available on the development of solid dispersion of divalproex sodium. Hence an attempt has been made for its development.
In the present study divalproex sodium solid dispersions were prepared by solvent evaporation method using various hydrophilic polymers like HPMC, PVPK30 and PEG6000.

The preparations were evaluated for its solubility studies, drug content, % yield, drug polymer interaction studies and in-vitro dissolution. The release studies reveal that there was an increase in the solubility of drug as solid dispersions when compared with pure drug in 0.1N HCL and HPMC shown high dissolution rate when compared to other polymers. This may probably due to high solubility of the drug by the carrier in the medium, particle size reduction in the course of the solid dispersion preparation, polymorphic transformation of drug crystals and chemical interactions between drug and carrier when compared to other polymers.

## Conclusion

Thus the present study concludes that the solid dispersion of poorly soluble divalpreox sodium with HPMC as water soluble carrier could be beneficial for the treatment of epilepsy with improved dissolution and absorption, hence it improves the bioavailability of the drug in the dissolution medium.

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